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EXAMINER
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1632	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/757,054	PETITTE ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's arguments filed 4-28-03, paper number 6, have been fully considered but they are not persuasive. Claim 55 has been added. Claims 44-55 are pending and under consideration in the instant office action. It is unclear why applicants believe claims 49 and 50 are withdrawn as stated in the status of the claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

1. Claims 44-54 remain rejected and claim 55 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification did not contemplate culturing avian PGCs for one or two months. Applicants did not contemplate isolating PGCs and stromal cells at the same time from avian embryos after stage 14 combined with a "preconditioned feeder matrix." The specification did not contemplate culturing avian feeder cells isolated from the gonad/genital ridge with PGCs isolated from embryos later than stage 14. Nor did the specification teach the culture conditions required to maintain PGCs in culture for one or two months in the presence of avian feeder cells isolated from the gonad/genital ridge. Applicants cite pg 5, line 3-10, pg 13, line 21 through pg

14, line 19 and claims 1-43 as originally filed which do not contemplate the combination of elements claimed for reasons of record.

Applicants argue combining PGCs, stromal cells and a preconditioned feeder matrix has support in Example 2 (pg 20; pg 5 of response). Applicants' argument is not persuasive. While Example 2, specifically pg 20, line 14-17, describes culturing gonadal PGCs and "preconditioned" STO feeder cells, STO cells are mouse fibroblasts. STO cells are not stromal cells, avian cells, isolated from an embryo, specifically after stage 14, or isolated at the same time as PGCs as claimed. Pg 8, lines 12-14, (pg 5 of response) teaches avian PGCs isolated "in accordance with the present invention also comprise a significant number of stromal cells." The citation does not suggest culturing PGCs and stromal cells on a preconditioned feeder matrix. In addition, pg 8, line 15-16, describes the isolation of both cells together as a "complication development of the process of the present invention," and, thus, teaching away from isolating PGCs and stromal cells at the same time combined with a preconditioned feeder matrix.

Applicants argue isolating stromal cells from an avian embryo after stage 14 or combining stromal cells isolated from an avian embryo with PGCs has support on pg 8, lines 12-14, and pg 10, lines 3-8 (pg 6 of response). Applicants argument is not persuasive. Pg 8, lines 12-14, teaches avian PGCs isolated "in accordance with the present invention also comprise a significant number of stromal cells." The citation does not suggest culturing PGCs and stromal cells isolated from an embryo after stage 14. In addition, pg 8, line 15-16, describes the isolation of both cells together as a "complication development of the process of the present invention,"

and, thus, teaching away from isolating PGCs and stromal cells from an embryo after stage 14 at the same time as being part of the invention. Pg 10, lines 3-8, (pg 6 of response) merely states cells may be isolated from an embryo after stage 14 and does not state stromal cells are isolated from an embryo after stage 14 or that PGCs and stromal cells are isolated together from an embryo after stage 14.

Applicants argue that one sentence is not needed to describe that which is clearly described in the specification (pg 6 of response). It is assumed that applicants mean one sentence is not need to describe that which is claimed. The examiner agrees; however, applicants' argument is not persuasive. The specification must reasonably put together the essential elements of the claimed invention. In this case, applicants rely on citations which do not share significant similarly. The citations are, in fact, incongruous with the claimed invention. Example 2 does not relate to isolating stromal cells from an avian, from an embryo, specifically after stage 14, or together with PGCs as in claim 44. Example 2 does not relate to a "preconditioned feeder matrix" from an avian or from an embryo, specifically after stage 14. While pg 8, lines 12-14, states isolating PGCs results in isolating stromal cells, the citation does not suggest culturing PGCs and stromal cells on a preconditioned feeder matrix, and describes the isolation of both cells together as a "complication development of the process of the present invention." Thus, the specification teaches away from the claimed invention. As such, the diversity and disparity between the citations do not lead one of skill to believe that applicants

contemplated isolating PGCs and stromal cells at the same time from embryos after stage 14 combined with a "preconditioned feeder matrix" as claimed.

Applicants' argument on pg 7, para. 1, is unclear. Pg 8, lines 12-14, is discussed above.

Applicants argue isolating cells anywhere from the embryo is not encompassed by claim 44 (pg 7, para. 2). Applicants' argument is not persuasive. While the specification teaches isolating PGCs from the genital ridge on pg 10, lines 22-24, the claim is not limited to isolating cells from the genital ridge or gonad of an embryo. The specification does not suggest isolating PGCs from anywhere within an embryo as broadly claimed.

Applicants argument bridging pg 7-8 is that pg 10, line 14 taken with pg 10, line 22-24, supports isolating PGC from the genital ridge or gonad. Applicants argument is not persuasive. While pg 10, line 14-16, states "embryonic gonadal PGCs and stromal cells may be collected from the embryonic gonads," and lines 22-24 teaches it was known that PGCs were known to be collected from the embryonic genital ridge or gonad, the citations do not support the breadth of isolating PGCs and stromal cells together from anywhere within an avian embryo as broadly claimed.

Pg 11, lines 3-10, does not teach stromal cells are isolated from the genital ridge (pg 8 of response). Applicants' argument is not persuasive because pg 10, lines 12-14, discusses when the embryo is obtained from fertilized eggs ("more preferably for about 96 to about 168 hours...") and does not relate to isolating stomal cells from an embryo.

Pg 11, lines 13-15, supports a feeder matrix derived from the gonad, but not a feeder matrix derived from the gonad that is preconditioned as claimed. Applicants point to pg 11-12 which states it is preferred that the feeder matrix is "preconditioned" (para. bridging pg 8-9 of response). Applicants argument is persuasive.

Applicants argue pg 11, lines 13-15, supports a feeder matrix from the gonad (pg 9, para. 1). Applicants argument is persuasive. However, the specification does not support isolating a feeder matrix from the genital ridge (claim 48) or claim "gonadal cells" (claim 49).

Applicants argue pg 11, lines 13-15, taken with pg 10, lines 22-24 support isolating a feeder matrix from the genital ridge (claim 48; pg 9, para. 2 of response). Pg 11, lines 13-15, support a feeder matrix isolated from the tissue from which the PGCs are isolated, e.g. the gonad. Pg 10, lines 22-24, states "Prior to the disclosure of the present invention, it was the general view among those of ordinary skill in the art that avian embryonic gonadal cells comprising primordial germ cells, such as may be collected from, for example, the avian embryonic genital ridge or gonad." Applicants argument is persuasive.

Applicants argue any of the cells isolated in the invention may be obtained from an embryo "after stage 14, more preferably stage 14 to stage 45..." (Pg 10, lines 3-8; pg 10, para. 1 of response). Applicants argument is not persuasive. "The invention relates to undifferentiated avian cells expressing an embryonic stem cell phenotype in general, and particularly relates to avian primordial germ cells and undifferentiated avian cells expressing an embryonic stem cell phenotype" (pg 1, line 5 of specification). Thus, stromal cells and feeder matrix cells are not

included in the "cells isolated in the invention." The method comprises "collecting avian cells comprising primordial germ cells from an avian embryo... ...depositing the avian cells in contact with a preconditioned feeder matrix..." (Pg 3, line 20, of specification). While stromal cells are found in avian gonadal cells comprising PGCs (pg 8, lines 12-14), nowhere does the specification imply the "preconditioned feeder matrix" cells are isolated from an avian embryo after stage 14 as claimed or part of the "cells isolated in the invention." Pg 10, lines 3-8, does not imply that "cells isolated in the invention" are the "preconditioned feeder matrix" cells on pg 11, line 11-16.

Applicants argue the rejection regarding support for sustaining the ES cell phenotype for one or two months is not proper because the examiner has not supported the contention that the ES cells phenotype is not sustained for the entire time that the culture is sustained, i.e. one or two months (pg 10, para. 2 of response). Applicants argument is not persuasive. Pg 14, lines 4-7, states "[t]he avian embryo cells of the present invention can be cultured for at least one or two months as is typical for a primary cell culture, which is significantly greater than the usual two week life of primary cultures of cells from an unincubated avian embryo." The citation merely suggests culturing avian embryo cells for one or two months and does not explicitly or implicitly suggest the ES cell phenotype is sustained for one or two months as claimed. It is not readily apparent that applicants thought the ES cell phenotype could be sustained for one or two months as claimed.

2. Claims 44-54 remain rejected and claim 55 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a culture comprising PGCs and avian feeder cells does not reasonably provide enablement for culturing PGCs and avian feeder cells for one or two months. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claims 53 and 54 require culturing the PGCs for more than a month or two months. At the time of filing, Ponce De Leon (1997, Revista Brasileira de Reproducao Animal, Vol. 21, pg 96-101) taught LIF, bFGF, IGF and SCF are required for long term culture of avian PGCs. However, the art did not teach how to culture avian PGCs in the presence of avian feeder cells for one or two months. The specification does not teach how to culture avian PGCs in the presence of avian feeder cells for one or two months. Given the teachings in the specification taken with the guidance provided in the specification, it would require one of skill in the art undue experimentation to determine how to maintain avian PGCs in the presence of avian feeder cells for one or two months.

The specification does not enable obtaining culturing PGCs having an ES cell phenotype for at least one or two months as broadly claimed. An ES cell is considered a cell capable of becoming both a somatic and germ cell upon being introduced into an embryo (pg 1, line 17). Simkiss (1990, 4th World Congr. Genetic Appl. Livestock Prod., Vol. 16, pg 111-114) and Petitte (1990, Development, Vol. 108, pg 185-195) taught chicken PGCs capable of producing

somatic and germ cell chimeric chickens. The stage of isolation and culture conditions required to maintain chicken ES cells for at least a month or two are not taught in the art or the specification. The stage and conditions required to obtain ES cells in species other than chickens are not taught in the art or the specification. Given the teachings in the art taken with the teachings in the specification, it would have required one of skill undue experimentation to isolate any avian ES cell other than chicken ES cells or to maintain any ES cell for one or two months as broadly claimed.

Applicants argue, as required by In re Marzocci, the examiner has not met his burden. Applicants argue an "inappropriate standard for measuring enablement has been adopted" and that the invention must be enabled so a person of skill in the art could make and use the invention from the disclosure taken with what was known in the art without 'undue experimentation. In re Wands...." (pg 12 of response). Applicants' arguments are not persuasive. The examiner has discussed the breadth of claim as encompassing culturing avian ES cells for one or two months, has provided numerous references establishing what was known in the art at the time of filing and has established that the stage of isolation and culture conditions required to maintain ES cells for at least one or two months as claimed was not known in the art. The examiner has established that the specification does not describe the stage of isolation and culture conditions required to maintain ES cells for at least one or two months as claimed or provide any working examples of such. The examiner has established that it would have required one of skill undue experimentation to isolate any avian ES cell other than chicken ES cells or to maintain any ES

cell for one or two months as broadly claimed. The burden required to establish a prima facie case of non-enablement has been met by the examiner. Applicants have not provided any specific arguments to facts established by the examiner.

Applicants argue the amount of experimentation required to isolate any avian ES cell other than chicken ES cells or to maintain any ES cell for one or two months as claimed would not be undue. Applicants argument is not persuasive. In view of the dearth of information in the art at the time of filing required for one of skill to isolate any avian ES cell other than chicken ES cells or to maintain any ES cell for one or two months as claimed, the parameters required to obtain such a result are essential to the invention. Because the specification does not teach the essential elements required to obtain results not known in the art, the amount of experimentation required by one of skill to obtain such results is, by its very nature, undue. Applicants point to Examples 1 and 2 (pg 13 of response) which merely reiterate parameters known in the art. Applicants point to pg 4, line 18-20, pg 8, lines 20-22 and pg 12, lines 4-8 which merely list avian species. The teachings cited do not overcome the unpredictability in the art by providing the specific conditions required to isolate any avian ES cell other than chicken ES cells or to maintain any ES cell for one or two months as broadly claimed. The conditions described in the specification are not "a reasonable amount of guidance" because they are not distinguishable from conditions known in the art. The conditions described in the specification are not adequate for one of skill to determine the parameters required to obtain results not known in the art.

Therefore, it would have required one of skill undue experimentation to isolate any avian ES cell other than chicken ES cells or to maintain any ES cell for one or two months as claimed.

3. Claims 44-54 remain rejected and claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The cells encompassed by the phrase "undifferentiated avian cells expressing an embryonic stem cell phenotype" is unclear (claim 44). It is unclear if the cells merely share a phenotype in common with avian ES cells or if the cells are avian ES cells. The specification defines cells having an ES cell phenotype as having a large nucleus, prominent nucleolus and little cytoplasm. However, the specification does not define how large, prominent or little the nucleus, nucleolus and cytoplasm are. Therefore, the metes and bounds of cells encompassed by applicants' definition cannot be determined.

Applicants point to pg 9, lines 15-23, which states "undifferentiated avian cells expressing an embryonic stem cell phenotype" encompass cells derived from PGCs. Applicants' argument is not persuasive. The claims require culturing "undifferentiated avian cells expressing an embryonic stem cell phenotype"; the claims are not limited to culturing ES cells, cells having the characteristic described on pg 9, line 15-23, particularly to culturing totipotent cells. As written, the metes and bounds of culturing cells having a large nucleus, prominent nucleolus and little cytoplasm, as defined in the specification cannot be determined because "large,"

"prominent" or "little" are subjective terms. Neither the specification or the art at the time of filing define the metes and bounds of a "large nucleus," "a prominent nucleolus" or "little cytoplasm".

While "preconditioned feeder matrix" is defined on pg 11, line 20, and conditioned media is described on pg 13, line 10, and known in the art, it remains unclear how the "preconditioned feeder matrix" relates to the "conditioned media" as claimed (claim 44). It is unclear if "conditioned media" encompasses the "preconditioned feeder matrix" (which has growth factors) or if "conditioned media" is separate from (i.e. excludes) the "preconditioned feeder matrix." Applicants have not argued this aspect of the rejection.

Stromal cells were defined in the art as connective tissue cell of an organ or other structure (see definition of "stromal cells" http/cancerweb.ncl.ac.uk/cgi-bin/omd?stromal+cells). Connective tissue cells are "cellular elements of the fibrous and nonfibrous components of the various forms of connective tissue" http/cancerweb.ncl.ac.uk/cgi-bin/omd?connective+tissue+cells). Thus, the PGCs and stromal cells in claim 44 must be isolated from the avian embryo after stage 14, wherein the stromal cells are connective tissue cells and not PGCs. Therefore, the rejection regarding stromal cells has been withdrawn.

The rejection regarding "derived" has been withdrawn because the term was deleted in the amendment filed 11-27-02 in claims 49 and 50 and in the amendment filed 4-28-03 in claims 47 and 48.

It remains unclear how PGCs isolated from an embryo later than stage 14 are distinguished from PGCs isolated from a stage X or stage 14 embryo (claim 44, 47, 48). PGCs isolated from stage X, 14 and after stage 14 embryos have the same structure and function. As such, the structural/functional distinction of PGCs isolated after stage XIV as claimed cannot be determined.

In response applicants distinguish the H&H staging system and the EGK system. Applicants state the PGCs isolated from after stage 14 are distinguished because they are capable of becoming ES cells. Applicants point out that the stage refers to the embryo, not the cells. Applicants' discussion is not persuasive. The distinction between H&H and EGK staging does not address how PGCs isolated from before or after stage 14 are structurally or functionally different. No evidence PGCs isolated before stage 14 are also capable of becoming ES cells. The rejection is based on PGCs isolated from stage X embryos or stage 14 embryos having the same structure/function as PGCs isolated after stage 14. One of skill could not distinguish PGCs isolated from a stage 14 embryo from those isolated after stage 14 embryos because PGCs have the same structure and function.

The rejection regarding "gonadal cells" has been withdrawn for claims 45 and 47 because the phrase has been deleted. However, the term remains in claim 49. Therefore, the metes and bounds of "gonadal cells" (claim 49) and "genital ridge cells" remain indefinite (claim 46, 48 and 50). It remains unclear if the cells are isolated from the genital ridge or if the cells have some genital function. It is unclear how such cells isolated from an embryo later than stage 14 are

distinguished from genital ridge cells isolated from a stage X or stage 14 embryo. Applicants have not addressed this rejection.

Claims 45-46 are indefinite as newly amended. Claim 44 requires the PGCs and stromal cells are isolated together. Claims 45 and 46 limit from where the stromal cells are isolated and do not include the PGCs. For consistency and clarity, claims 45 and 46 should describe the PGCs and stromal cells as being isolated from the gonad or genital ridge of the avian embryo.

Claims 49 and 50 are indefinite because "the avian gonadal cells" and "the avian genital ridge cells" lack antecedent basis. In addition, claims 49 and 50 have an identical scope as claims 47 and 48, respectively, and are substantial duplicates.

The rejection of claim 52 has been withdrawn in view of the amendment filed 11-27-02.

The metes and bounds of "sustained" in claims 53 and 54 remains indefinite. The specification teaches "sustained" means capable of undergoing further cell division (pg 9, line 1). Claims 53 and 54 require the embryonic stem cell phenotype is "sustained" for at least one or two months. While a cell may undergo further cell division, a phenotype (a visible property) does not "undergo further cell division." Therefore, a "phenotype" that "undergoes further cell division" for at least one or two months as claimed does not make sense. Applicants arguments relate to cells being "sustained" for one or two months. Applicants' argument is not persuasive because the claim does not require the cells be "sustained" for one or two months.

Claim Rejections - 35 USC § 102

A PGC culture sustained for one or two months as claimed (claims 53, 54) does not differ from PGC cultures known in the art because their structure and functions are equivalent and because culturing PGCs for one or two months does not alter the structure or function of the culture. Therefore, the limitations in claims 53 and 54 do not bear patentable weight in considering the art because they does not distinguish the structure or function of the cells within the culture or the components of the culture from those known in the art.

Cells isolated from avian embryonic gonads or genital ridge contain both PGCs and fibroblasts, wherein said fibroblasts create a feeder layer in culture (see rejections below) which is equivalent to a "preconditioned feeder matrix" and "avian stromal cells" as claimed. Fibroblasts from the gonad or genital ridge are a "preconditioned feeder matrix" because they are present in the cell population before culturing. Fibroblasts from embryonic gonads or genital ridge are stromal because they are part of an organ or other structure (see definition of "stromal" http/cancerweb.ncl.ac.uk/cgi-bin/omd?stromal).

The PGCs in culture described below are "sustained" as claimed because they undergo cell division in culture (Allioli, Chang, Petitte) or because they are.

Isolating cells from the gonads or germinal ridge is equivalent to "genital ridge cells" or cells derived from genital ridge cells because gonads are made up of cells derived from the genital ridge.

4. Claims 44-54 remain rejected and claim 55 is rejected under 35 U.S.C. 102(b) as being anticipated by Allioli (1994, Devel. Biol., Vol. 165, pg 30-37) for reasons of record.

Allioli taught isolating chicken cells from the gonads of stage 27-28 embryos and culturing the cells in media. The sample contained PGCs as well as fibroblasts which created a feeder layer in culture. The PGCs of Allioli are capable of becoming germ cells, isolated from the germinal ridge of an avian blastoderm and are pluripotent which are all "ES cell phenotypes" as claimed. Allioli teaches adding steel factor, LIF and FGF to the culture (pg 31, col. 2; 34, col. 2, "gonadal cell culture"; pg 36, col. 1, 2nd para.). Thus, Allioli anticipates the claims.

Applicants argue ES cells are not germ cells. Applicants' argument is off point. The rejection is based PGCs having characteristics that are an "ES cell phenotype" as claimed. The claims require "cells expressing an embryonic cell phenotype;" the claims are not limited to ES cells or to totipotent cells.

5. Claims 44-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Chang (1995, Cell Biol. Internatl. Vol. 19. No. 2, pg 143-149).

Chang taught isolating stromal cells from the genital ridge of day 5 (stage 27-28) embryos. The cells were cultured in media containing IGF, FGF and LIF (pg 144, col. 1). These cells inherently contain PGCs (pg 144, col. 1 para. 4; col. 2, 3 lines from the bottom; pg 146, Fig. 2, "PGCs derived from 5-day embryonic ridge in culture"). The PGCs of Chang are capable of becoming germ cells, isolated from the germinal ridge of an avian blastoderm and pluripotent

which are all "ES cell phenotypes" as claimed. The cell culture was maintained for at least 4 days (pg 14, col. 1, 3rd para., line 5).

Chang also taught isolating PGCs from the blood of day 2 (stage 13-14) embryos and adding the day-2 PGCs to the cells isolated from the genital ridge (pg 144, col. 2, 3rd para.; col. 2, "Results"). PGCs isolated from stage 13-14 are equivalent to PGCs isolated later than stage 14 as claimed because they have the same structure and function. Therefore, avian PGCs collected from an avian embryo "later than stage 14" as claimed does not bear patentable weight because it does not distinguish the structure or function of the PGCs within the culture from those taught by Chang.

Applicants note that prior to the invention of the present application, "it was not perceived to be possible to provide a sustained culture of avian cells expressing a plurpotent embryonic stem cell phenotype that could be derived from PGCs isolated from a later than stage 14 embryo. Indeed it was believed that PGCs isolated from later than stage 14 embryos were destined for terminal differentiation into germ cells instead of other tissues." Applicants' note is acknowledged. However, the structure of function of PGCs isolated from before stage 14 and after stage 14 are the same.

Applicants argue "PGCs isolated from a later than stage 14 (H&H) embryo are distinguishable from PGCs from the blood of day 2 (stage 13-14) embryos because, by definition, stage 13-14 is not 'later than stage 14'." In other words, applicants argue PGCs isolated after stage 14 are distinguishable from stage 13-14 embryos because they are isolated from different

stages. Applicants' argument is not persuasive because the structure of function of PGCs isolated from before stage 14 and after stage 14 are the same.

Applicants argue ES cells are not germ cells. Applicants' argument is off point. The rejection is based PGCs having characteristics that are an "ES cell phenotype" as claimed. The claims require "cells expressing an embryonic cell phenotype;" the claims are not limited to ES cells or to totipotent cells.

6. Claims 44-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Chang (1997, Cell Biol. Internatl., Vol. 21, No. 8, pg 495-499).

Chang taught isolating germinal ridge stromal cells from day 5 (stage 27-28) embryos. The cells were cultured for 5 days in media containing IGF, FGF and LIF with germinal ridge stromal feeder cells isolated from day 5 embryos to obtain gPGCs. The gPGCs were injected into recipient embryos and provided germline transmission (pg 496, "Materials and Methods"; pg 497, Fig. 1, "Progeny of germline chimeric chickens"). The PGCs of Chang were capable of germline transmission which is an "ES cell phenotype" as claimed.

The rejection of claims 44-54 under 35 U.S.C. 102(e) as being anticipated by Petitte (US Patent 6,333,192) has been withdrawn because the instant application is a continuation of '192 and a terminal disclaimer has been filed over '192.

The rejection of claims 44-54 under 35 U.S.C. 102(e) as being anticipated by Petitte (US Patent 6,354,242) has been withdrawn because the instant application has an effective filing date of 8-9-99 which is prior to 3-23-00, the filing date of '242.

7. Claims 44-54 remain rejected and claim 55 is rejected under 35 U.S.C. 102(e) as being anticipated by Petitte (US Patent 5,340,740), Petitte (US Patent 5,656,479) or Petitte (US Patent 5,840,510) for reasons of record.

Petitte taught culturing all the cells from a stage X embryo and isolating PGCs ('740). The cells were seeded onto chicken embryonic fibroblast feeder layers and cultured with BRL conditioned medium (col. 7, lines 7-14, of '740; col. 6, line 44, of '479; col. 6, line 54-65, of '510). PGCs isolated from stage X are equivalent to PGCs isolated later than stage 14 as claimed because PGCs isolated from stage X and XIV have the same function. Therefore, avian PGCs collected from an avian embryo "later than stage 14" as claimed does not bear patentable weight because it does not distinguish the structure or function of the PGCs within the culture from those taught by Petitte. Thus, Petitte anticipates the claims.

Applicants argue the means of staging embryos used by Petitte was EGK and not the H&H staging system. Applicants' argument is not persuasive. Petitte does not disclose the staging system was EGK. More importantly, the argument is moot because the rejection is based on the fact that the structure and function of the culture described by Petitte is equivalent to that claimed.

Applicants note that prior to the invention of the present application, "it was not believed that PGCs later than stage 14 (H&H scale) could be used to culture pluripotent undifferentiated avian cells expressing an embryonic stem cell phenotype." Applicants' note is acknowledged.

However, the structure of function of PGCs isolated from stage X and after stage 14 have the same structure and function.

8. Claims 44-54 remain rejected and claim 55 is rejected under 35 U.S.C. 102(e) as being anticipated by Ponce de Leon (US Patent 6,156,569) for reasons of record.

Ponce de Leon taught isolating PGCs isolated from cells of stage XIV embryos. The cells were cultured with complete medium, LIF, FGF, IGF and SCF for at least 25 days (col. 7, line 43 through col. 8, line 53). The PGCs were pluripotent and capable of creating a chimeric chicken which is a phenotype of ES cells. PGCs isolated from stage XIV are equivalent to PGCs isolated after stage 14 as claimed because PGCs isolated from stage XIV and after stage XIV have the same structure and function. Therefore, avian PGCs collected from an avian embryo "later than stage 14" as claimed does not bear patentable weight because it does not distinguish the structure or function of the PGCs within the culture from those taught by Ponce de Leon. Thus, Ponce de Leon anticipates the claims.

Applicants argue stage XIV differs substantially from stages after XIV. Applicants argument is not persuasive because PGCs isolated from stage XIV or after stage XIV have the same structure and function.

Applicants note that prior to the invention of the present application, "it was believed that it was not possible to obtain pluripotent embryonic stem cells from avian primordial germ cells from an embryo later than stage 14." Applicants' note is acknowledged. However, the structure

of function of PGCs isolated from stage XIV and after stage 14 have the same structure and function.

Double Patenting

The rejection of claims 44-54 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 3, 13, 19 and 23 of copending Application No. 08/446,021 (now US Patent 6,515,199) has been withdrawn because the claims of '199 are limited to altering the phenotype of a bird using avian somatic tissue-specific stem cells and do not require avian PGCs having an ES cell phenotype as claimed in the instant application.

9. Claims 44-54 remain rejected and claim 55 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 21-27 of copending Application No. 09/094176 for reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the avian PGCs having an ES cell phenotype in the instant application are used in the method of '176. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants argue the cells used in '176 are not isolated from after stage 14. Applicants' argument is not persuasive because PGCs isolated after stage 14 have the same structure and function as those used in the method of '176. The stage during which the PGCs are isolated does

not bear patentable weight in the instant product claims because the product claimed has the same structure and function as the one used in the method of '176.

The rejection of claims 44-54 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 19, 35 of U.S. Patent No. 6,333,192 in view of Chang (1995, Cell Biol. Internat'l., Vol. 19, page 143-9) has been withdrawn in view of the terminal disclaimer filed 11-27-02.

10. Claims 44-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 8-10 of U.S. Patent No. 5,340,740 in view of Chang (1995, Cell Biol. Internat'l., Vol. 19, page 143-9).

Claims 1 and 8-10 claim a sustained culture of undifferentiated avian cells having an ES cell phenotype and methods of making such a culture. '740 did not claim culturing the cells on avian feeder cells or the cell culture made by the method.

However, at the time of filing, Chang taught culturing PGCs on avian stromal cells. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate avian cells having an ES cell phenotype as taught by '740, wherein the avian cells are cultured on avian feeder cells. One of ordinary skill in the art at the time the invention was made would have been motivated to use avian feeder cells to increase the number of PGCs as taught by Chang (abstract).

Applicants argue the cells taught by '740 in view of Chang were not isolated from after stage 14. Applicants' argument is not persuasive because PGCs isolated after stage 14 have the

same structure and function as those by '740 in view of Chang. The stage during which the PGCs are isolated does not bear patentable weight in the instant product claims because product claimed has the same structure and function as that described by '740 in view of Chang.

11. Claims 44-54 remain rejected and claim 55 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,656,479 or 5,830,510 in view of Chang (1995, Cell Biol. Internat'l., Vol. 19, page 143-9) for reasons of record.

Claim 1 of '479 and '510 are directed toward a sustained avian cell culture consisting essentially of undifferentiated avian cells expressing an embryonic cell phenotype. Claim 2 states the cells may be cultured on STO feeder cells in the presence of LIF. '479 and '510 did not claim culturing the cells on avian feeder cells.

However, at the time of filing, Chang taught culturing PGCs on avian stromal cells. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate avian cells having an ES cell phenotype as claimed in '479 and '510 wherein the avian cells are cultured on avian feeder cells. One of ordinary skill in the art at the time the invention was made would have been motivated to use avian feeder cells to increase the number of PGCs as taught by Chang (abstract).

Applicants argue the cells taught by '749 or '510 in view of Chang were not isolated from after stage 14. Applicants' argument is not persuasive because PGCs isolated after stage 14 have the same structure and function as those by '749 or '510 in view of Chang. The stage during

which the PGCs are isolated does not bear patentable weight in the instant product claims because product claimed has the same structure and function as that described by '749 or '510 in view of Chang.

12. Claims 44-54 remain rejected and claim 55 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,156,659 in view of Chang (1995, Cell Biol. Internat'l., Vol. 19, page 143-9) for reasons of record.

Claims 1-12 of '659 claim a method of culturing undifferentiated avian cells having an ES cell phenotype for at least 14 days using LIF, bFGF, IGF and SCF . '659 did not claim culturing the cells on avian feeder cells.

However, at the time of filing, Chang taught culturing PGCs on avian stromal cells isolated from the genital ridge of Stage 27-28 embryos. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to isolate avian cells having an ES cell phenotype as taught by '659, wherein the avian cells are cultured on avian feeder cells. One of ordinary skill in the art at the time the invention was made would have been motivated to use avian feeder cells to increase the number of PGCs as taught by Chang (abstract).

Applicants argue the cells taught by '659 in view of Chang were not isolated from after stage 14. Applicants' argument is not persuasive because PGCs isolated after stage 14 have the same structure and function as those by '659 in view of Chang. The stage during which the

PGCs are isolated does not bear patentable weight in the instant product claims because product claimed has the same structure and function as that described by '659 in view of Chang.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

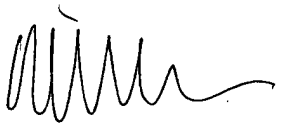
Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER

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Related Cell Culture Products

Comments:	The line was derived from the SIM fibroblast line. Cells are resistant to 6-thioguanine and ouabain and are HGPRT- (HPRT-) and HAT sensitive. The line is used to prepare feeder layers for teratocarcinoma cells, hybridomas and embryonic stem cells. Tested and found negative for ectromelia virus (mousepox).
Age Stage:	embryo
Propagation:	ATCC medium: Dulbecco's modified Eagle's medium with 4 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate and 4.5 g/L glucose, 90%; fetal bovine serum, 10% Temperature: 37.0 C
Subculturing:	Remove medium, and rinse with 0.25% trypsin, 0.03% EDTA solution. Remove the solution and add an additional 1 to 2 ml of trypsin-EDTA solution. Allow the flask to sit at room temperature (or at 37C) until the cells detach. Add fresh culture medium, aspirate and dispense into new culture flasks.
Split Ratio:	A subcultivation ratio of 1:3 to 1:10 is recommended

Fluid Renewal:	2 to 3 times per week
Related Products:	Recommended medium (without the additional supplements or serum described under ATCC Medium) - ATCC No: 30-2002 recommended serum - ATCC No: 30-2020 irradiated to be used as feeder cells - ATCC No: 56-X
References:	1070: Martin GR , Evans MJ . Differentiation of clonal lines of teratocarcinoma cells: formation of embryoid bodies in vitro. Proc. Natl. Acad. Sci. USA 72: 1441-1445, 1975. PubMed: 1055416 21874: , editors. Teratomas and differentiation. New York: Academic Press; 1975, pp. 169-187. 22387: Cell 6: 467-474, 1975. 22701: Martin GR , et al. The development of cystic embryoid bodies in vitro from clonal teratocarcinoma stem cells. Dev. Biol. 61: 230-244, 1977. PubMed: 590624

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